

## P ENT COOPERATION TREA

PCT

From the INTERNATIONAL BUREAU

NOTIFICATION OF THE RECORDING  
OF A CHANGE(PCT Rule 92bis.1 and  
Administrative Instructions, Section 422)

To:

MASCHIO, Antonio  
D Young & Co  
21 New Fetter Lane  
London EC4A 1DA  
ROYAUME-UNI

Date of mailing (day/month/year) 06 February 2002 (06.02.02)	<b>IMPORTANT NOTIFICATION</b>
Applicant's or agent's file reference P7615WO ATM	
International application No. PCT/GB00/03450	International filing date (day/month/year) 08 September 2000 (08.09.00)

## 1. The following indications appeared on record concerning:

☒ the applicant      ☒ the inventor      ☐ the agent      ☐ the common representative

Name and Address SEPP, Tiina MRC Laboratory for Molecular Biology Hills Road Cambridge CB2 2QH United Kingdom	State of Nationality GB	State of Residence GB
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

## 2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☐ the person      ☐ the name      ☐ the address      ☒ the nationality      ☐ the residence

Name and Address SEPP, Tiina MRC Laboratory for Molecular Biology Hills Road Cambridge CB2 2QH United Kingdom	State of Nationality EE	State of Residence GB
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

## 3. Further observations, if necessary:

## 4. A copy of this notification has been sent to:

<input checked="" type="checkbox"/> the receiving Office	<input type="checkbox"/> the designated Offices concerned
<input type="checkbox"/> the International Searching Authority	<input checked="" type="checkbox"/> the elected Offices concerned
<input type="checkbox"/> the International Preliminary Examining Authority	<input type="checkbox"/> other:

<b>The International Bureau of WIPO</b> 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35	Authorized officer Kari HUYNH-KHUONG Telephone No.: (41-22) 338.83.38
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<b>International application No.</b> PCT/GB00/03450	<b>International filing date (day/month/year)</b> 08 September 2000 (08.09.00)

## 1. The following indications appeared on record concerning:

☒ the applicant    ☒ the inventor    ☐ the agent    ☐ the common representative

<b>Name and Address</b> HOLLIGER, Philipp MRC Laboratory for Molecular Biology Hills Road Cambridge CB2 2QH United Kingdom	<b>State of Nationality</b> GB	<b>State of Residence</b> GB
	<b>Telephone No.</b>	
	<b>Facsimile No.</b>	
	<b>Teleprinter No.</b>	

## 2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☐ the person    ☐ the name    ☐ the address    ☒ the nationality    ☐ the residence

<b>Name and Address</b> HOLLIGER, Philipp MRC Laboratory for Molecular Biology Hills Road Cambridge CB2 2QH United Kingdom	<b>State of Nationality</b> CH	<b>State of Residence</b> GB
	<b>Telephone No.</b>	
	<b>Facsimile No.</b>	
	<b>Teleprinter No.</b>	

## 3. Further observations, if necessary:

## 4. A copy of this notification has been sent to:

<input checked="" type="checkbox"/> the receiving Office	<input type="checkbox"/> the designated Offices concerned
<input type="checkbox"/> the International Searching Authority	<input checked="" type="checkbox"/> the elected Offices concerned
<input type="checkbox"/> the International Preliminary Examining Authority	<input type="checkbox"/> other:

<b>The International Bureau of WIPO</b> 34, chemin des Colombettes 1211 Geneva 20, Switzerland	<b>Authorized officer</b>  Kari HUYNH-KHUONG
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

## P ENT COOPERATION TREA

PCT

## NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Commissioner  
 US Department of Commerce  
 United States Patent and Trademark  
 Office, PCT  
 2011 South Clark Place Room  
 CP2/5C24  
 Arlington, VA 22202  
 ETATS-UNIS D'AMERIQUE  
 in its capacity as elected Office

Date of mailing (day/month/year) 20 June 2001 (20.06.01)	
International application No. PCT/GB00/03450	Applicant's or agent's file reference P7615WO ATM
International filing date (day/month/year) 08 September 2000 (08.09.00)	Priority date (day/month/year) 08 September 1999 (08.09.99)
Applicant HOLLIGER, Philipp et al	

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:

26 March 2001 (26.03.01)

☐ in a notice effecting later election filed with the International Bureau on:

2. The election ☒ was  
☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer  Olivia TEFY
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference P7615WO ATM		<b>FOR FURTHER ACTION</b> See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/GB00/03450	International filing date (day/month/year) 08/09/2000	Priority date (day/month/year) 08/09/1999	
International Patent Classification (IPC) or national classification and IPC C12Q1/68			
Applicant MEDICAL RESEARCH COUNCIL et al.			

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.


2. This REPORT consists of a total of 7 sheets, including this cover sheet.

☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of 6 sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☒ Certain defects in the international application
- VIII ☒ Certain observations on the international application

Date of submission of the demand  26/03/2001	Date of completion of this report  10.12.2001
Name and mailing address of the international preliminary examining authority:   European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer  Leber, T  Telephone No. +49 89 2399 7195



# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB00/03450

## I. Basis of the report

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):

### Description, pages:

1-31 as originally filed

### Claims, No.:

1-27 as received on 12/11/2001 with letter of 09/11/2001

### Drawings, sheets:

1/5-5/5 as originally filed

### Sequence listing part of the description, pages:

1-5, filed with the letter of 02.11.2000

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☒ furnished subsequently to this Authority in written form.
- ☒ furnished subsequently to this Authority in computer readable form.
- ☒ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☒ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB00/03450

- ☐ the description,      pages:
- ☐ the claims,      Nos.:
- ☐ the drawings,      sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

*(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)*

6. Additional observations, if necessary:

## V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

### 1. Statement

Novelty (N)	Yes:	Claims	1-27
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-27
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-27
	No:	Claims	

2. Citations and explanations  
**see separate sheet**

## VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:  
**see separate sheet**

## VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:  
**see separate sheet**

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

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International application No. PCT/GB00/03450

**R Item I**

**Basis of the opinion**

1. Sequence listings pages 1-5 filed with the letter of 02.11.2000 do not form part of the application (Rule 13<sup>ter</sup>.1(f) PCT).

**Re Item V**

**Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

**1. Basis for the assessment of novelty, inventive step and industrial applicability**

- 1.1 Reference is made to the following document/s/:

D1: WO 98 25947 A (SQUIBB BRISTOL MYERS CO) 18 June 1998 (1998-06-18)

- 1.2 The amendments filed with letter of 09.11.2001 fulfil the requirements of Art 34(2)(b) PCT.

**2. Novelty**

- 2.1 Independent claims 1, 5 and 9 are novel over the prior art cited in the ISR as none of the documents referred to therein disclose a method suitable for studying molecular interactions involving the protein  $\sigma 54$  (Art 33(2) PCT). The dependent claims 2-4, 6-8 and 10-27 are thus also novel (Art 33(2) PCT).

**3. Inventive step**

- 3.1 Document D1 discloses a prokaryotic two hybrid system suitable for e.g. interaction cloning, mapping protein interaction etc. The method encompasses a prokaryotic host cell, a first fusion protein having a first DNA-binding domain and a first interaction domain, a second fusion protein having a second DNA-binding

domain and a second interacting domain capable of binding to the first interacting domain, a nucleic acid molecule having (i) a reporter gene operatively linked to a promoter, (ii) a first operator site capable of binding to the first DNA-binding domain and (iii) a second operator site capable of binding the second DNA-binding domain, whereby binding of the first interacting domain to the second interacting domain is signalled by altered expression of the reporter gene (D1, Abstract; claim 1).

- 3.2 Claim 1 differs from the closest prior art document D1 in that a specific regulatory system consisting of  $\sigma 54$  and an activator of  $\sigma 54$  is used to study the protein-nucleic acid interaction. The technical problem is to provide an alternative method for interaction studies. The solution provided in claim 1 is to take advantage of the interaction between  $\sigma 54$  and an activator of  $\sigma 54$  for initiation of transcription. It appears that an inventive step (Art 33(3) PCT) can be acknowledged for said solution as none of the documents cited in the ISR disclose or indicate that the interaction between  $\sigma 54$  and an activator of  $\sigma 54$  can be used for said purpose. The dependent claims 2-4 are thus also inventive (Art 33(3) PCT). Independent claims 5 and 9 refer to similar technical problems as claim 1 and provide solutions also based on the interaction between  $\sigma 54$  and an activator of  $\sigma 54$ . Therefore, these claims and the claims dependent thereon (claims 6-8 and 10-27) are also inventive (Art 33(3) PCT).

#### **4. Industrial applicability**

- 4.1 The subject-matter disclosed in the claims 1-27 of the present application appears to be industrially applicable (Art 33(4) PCT).

#### **Re Item VII**

##### **Certain defects in the international application**

1. The expression "herein incorporated by reference" or equivalents thereof (e.g. page 31, lines 4-6) in the description of the present application should be deleted (Guidelines, Section IV, II-4.17).



2. The vague and imprecise statement in the description of the present application (page 31, lines 8-15) implies that the subject-matter for which protection is sought may be different to that defined by the claims, thereby resulting in lack of clarity of the claims (Art. 6 PCT) when used to interpret them (Guidelines, Section IV, III-4.3a). The statement should therefore have been amended to remove this inconsistency.
3. To meet the requirements of Art 5 and Rule 5 PCT, the document D1 should have been identified in the description and the relevant background art disclosed therein should be briefly discussed if the subject-matter for which this document is relevant prior art remains in the claims.

**Re Item VIII**

**Certain observations on the international application**

1. According to the description, the methods disclosed in the present application are intended for in vivo and in vitro use (page 5, lines 13-18). It appears, however, that the in vivo application is limited to prokaryotes (page 2, lines 9-10; page 16, line 29). This limiting feature is missing in the independent claims 1, 5 and 9 (Guidelines, Section IV, III-4.4). The same objection also applies to claim 25.
2. The term "heterologous" lacks clarity (Art 6 PCT) as it is not clear with respect to which organism the "nucleic acid binding sequence" is heterologous (see also point 1 above). Moreover, claim 1 in its present form suggests a "hybrid  $\sigma$ 54 activator **protein**" which comprises a "nucleic acid binding **sequence**". This feature lacks support by the description (Art 6 PCT). What appears to be meant is a "nucleic acid binding **domain**" (Fig. 1A; page 26, lines 5-6). The same objection applies to claims 5 and 9.
3. The abbreviation "IHF" in claim 9 should have been defined in the claim (Art 6 PCT).
4. The term "constitutively active  $\sigma$ 54 transcription activating domain" referred to in claim 1 appears to indicate that even in absence of an activator of  $\sigma$ 54,

transcription could start. This, however, appears to go against the principle of the present invention, namely that it is the interaction between  $\sigma 54$  and an activator of  $\sigma 54$  which causes the transcription to start (page 19 "G: Configurations of the invention"; claim 1b)) and thus results in a lack of clarity (Art 6 PCT).

5. The word "in" appears to be missing in claim 11 (Art 6 PCT).
6. The word "acid" appears to be missing in claim 12 (Art 6 PCT).
7. Claims should be defined by technical features (Rule 6.3a PCT). The list referred to in claim 14 does not fulfil this requirement as database accession numbers are no technical features. In its present form, the list represents only internal designations unknown to the skilled person. Moreover, the description of a patent application shall indicate background art which is useful for understanding, searching and examination of the invention (Rule 5.1(a)(ii) PCT). As the database accession numbers represent sequences which do not follow Rule 13ter for sequence listing, said sequences cannot be searched and examined. Moreover, database entries may change over time, thus there appears to be a lack of reproducibility (Art 5 PCT).
8. The expression "proteins conferring another selectable marker" in claim 22 lacks support by the description (Art 6 PCT).
9. Claims 23 and 24 refers to compounds. These compounds, however, are only defined by the result to be achieved and not, as required by the PCT (Rule 6.3(a) PCT) by technical features. This results in a lack of clarity and support by the description (Art 6 PCT).

## PATENT COOPERATION TREATY

## PCT

## INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference <b>P7615W0 ATM</b>	<b>FOR FURTHER ACTION</b> see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. <b>PCT/GB 00/ 03450</b>	International filing date (day/month/year) <b>08/09/2000</b>	(Earliest) Priority Date (day/month/year) <b>08/09/1999</b>
Applicant <b>MEDICAL RESEARCH COUNCIL</b>		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 2 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

## 1. Basis of the report

- a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

- b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☒ furnished subsequently to this Authority in written form.

☒ furnished subsequently to this Authority in computer readable form.

☒ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☒ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☐ **Certain claims were found unsearchable** (See Box I).

3. ☐ **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No.

☐ as suggested by the applicant.

☒ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

1

☐ None of the figures.

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/00/03450

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C12Q1/68 G01N33/50 C12N15/10

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C12Q G01N C12N C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, CHEM ABS Data, MEDLINE, EMBASE, BIOSIS

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 98 25947 A (SQUIBB BRISTOL MYERS CO) 18 June 1998 (1998-06-18) claims 1-24 ---	1-27
A	WO 99 28746 A (LADANT DANIEL ;ULLMANN AGNES (FR); KARIMOVA GOUZEL (FR); PASTEUR I) 10 June 1999 (1999-06-10) claim 1 -----	1-27

☐ Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

## ° Special categories of cited documents :

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

- \*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- \* & \* document member of the same patent family

Date of the actual completion of the international search

2 July 2001

Date of mailing of the international search report

11/07/2001

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+31-70) 340-3016

Authorized officer

Gabriels, J

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 00/03450

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9825947 A	18-06-1998	AU 721549 B AU 5599398 A EP 0963376 A US 6051381 A	06-07-2000 03-07-1998 15-12-1999 18-04-2000
WO 9928746 A	10-06-1999	EP 1036323 A	20-09-2000